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(2 AND (@PY <= "1998")).PGPB,USPT,USOC,EPAB,JPAB,DWPI.	0
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Search History

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L3	L2 and @py<=1998	0	L3
L2	L1 same (transmembrane domain)	148	L2
L1	(beta-secretase)	1033	L1

END OF SEARCH HISTORY

L2: Entry 147 of 148 File: USPT Jul 16, 2002

DOCUMENT-IDENTIFIER: US 6420534 B1
TITLE: Alzheimer's disease secretase, APP substrates therefor, and uses thereof

Brief Summary Text (27):
In one preferred embodiment, the APP protein or fragment thereof further includes an APP transmembrane domain carboxy-terminal to the APP-Sw .beta.-secretase peptide sequence. Polypeptides that include the TM domain are particularly useful in cell-based APP processing assays. In contrast, embodiments lacking the TM domain are useful in cell-free assays of APP processing.

Brief Summary Text (30):
In another, related embodiment, the invention provides a polypeptide useful for assaying for modulators of .beta.-secretase activity, said polypeptide comprising an amino acid sequence of the formula NH.sub.2 -X-Y-Z-KK-COOH; wherein X Y, and Z each comprise an amino acid sequence of at least one amino acid; wherein --NH.sub.2 -X comprises an amino-terminal amino acid sequence having at least one amino acid residue; wherein Y comprises an amino acid sequence of a .beta.-secretase recognition site of a mammalian amyloid protein precursor (APP); and wherein Z-KK-COOH comprises a carboxy-terminal amino acid sequence ending in two lysine (K) residues. In one preferred variation, the carboxyl-terminal amino acid sequence Z includes a hyrdrophobic domain that is a transmembrane domain in host cells that express the polypeptide. Host cells that express such a polypeptide are particularly useful in assays described herein for identifying modulators of APP processing. In another preferred variation, the amino-terminal amino acid sequence X includes an amino acid sequence of a reporter or marker protein, as described above. In still another preferred variation, the .beta.-secretase recognition site Y comprises the human APP-Sw .beta.-secretase peptide sequence NLDA. It will be apparent that these preferred variations are not mutually exclusive of each other--they may be combined in a single polypeptide. The invention further provides a polynucleotide comprising a nucleotide sequence that encodes such polypeptides, vectors which comprise such polynucleotides, and host cells which comprises such vectors, polynucleotides, and/or polypeptides.

Brief Summary Text (33):
In a related aspect, the invention provides a method for assaying for modulators of .beta.-secretase activity, comprising the steps of: (a) contacting a first composition with a second composition both in the presence and in the absence of a putative modulator compound, wherein the first composition comprises a mammalian .beta.-secretase polypeptide or biologically active fragment thereof, and wherein the second composition comprises a substrate polypeptide having an amino acid sequence comprising a .beta.-secretase cleavage site; (b) measuring cleavage of the substrate polypeptide in the presence and in the absence of the putative modulator compound; and (c) identifying modulators of .beta.-secretase activity from a difference in cleavage in the presence versus in the absence of the putative modulator compound. A modulator that is a .beta.-secretase antagonist (inhibitor) reduces such cleavage, whereas a modulator that is a .beta.-secretase agonist increases such cleavage. Since such assays are relevant to development of Alzheimer's disease therapeutics for humans, it will be readily apparent that, in one preferred embodiment, the first composition comprises a purified human Asp2 polypeptide. In one variation, the first Composition comprises a soluble fragment

of a human Asp2 polypeptide that retains Asp2 .beta.-secretase activity. Several such fragments (including .DELTA.TM fragments) are described herein in detail. Thus, in a particular embodiment, the soluble fragment is a fragment lacking an Asp2 transmembrane domain.

Detailed Description Text (17):
Also provided herein are purified Hu-Asp polypeptides, both recombinant and non-recombinant. Most importantly, methods to produce Hu-Asp2 polypeptides in active form are provided. These include production of Hu-Asp2 polypeptides and variants thereof in bacterial cells, insect cells, and mammalian cells, also in forms that allow secretion of the Hu-Asp2 polypeptide from bacterial, insect or mammalian cells into the culture medium, also methods to produce variants of Hu-Asp2 polypeptide incorporating amino acid tags that facilitate subsequent purification. In a preferred embodiment of the invention the Hu-Asp2 polypeptide is converted to a proteolytically active form either in transformed cells or after purification and cleavage by a second protease in a cell-free system, such active forms of the Hu-Asp2 polypeptide beginning with the N-terminal sequence TQHGIR (SEQ ID NO:69) or ETDEEP. The sequence TQHGIR represents the amino-terminus of Asp2(a) or Asp2(b) beginning with residue 22 of SEQ ID NO: 4 or 6, after cleavage of a putative 21 residue signal peptide. Recombinant Asp2(a) expressed in and purified from insect cells was observed to have this amino terminus, presumably as a result of cleavage by a signal peptidase. The sequence ETDEEP represents the amino-terminus of Asp2(a) or Asp2(b) beginning with residue 46 of SEQ ID NO: 4 or 6, as observed when Asp2(a) has been recombinantly produced in CHO cells (presumably after cleavage by both a rodent signal peptidase and another rodent peptidase that removes a propeptide sequence). The Asp2(a) produced in the CHO cells possesses .beta.-secretase activity, as described in greater detail in Examples 11 and 12. Variants and derivatives, including fragments, of Hu-Asp proteins having the native amino acid sequences given in SEQ ID Nos: 2, 4, and 6 that retain any of the biological activities of Hu-Asp are also within the scope of the present invention. Of course, one of ordinary skill in the art will readily be able to determine whether a variant, derivative, or fragment of a Hu-Asp protein displays Hu-Asp activity by subjecting the variant, derivative, or fragment to a standard aspartyl protease assay. Fragments of Hu-Asp within the scope of this invention include those that contain the active site domain containing the amino acid sequence DTG, fragments that contain the active site domain amino acid sequence DSG, fragments containing both the DTG and DSG active site sequences, fragments in which the spacing of the DTG and DSG active site sequences has been lengthened, fragments in which the spacing has been shortened. Also within the scope of the invention are fragments of Hu-Asp in which the transmembrane domain has been removed to allow production of Hu-Asp2 in a soluble form. In another embodiment of the invention, the two halves of Hu-Asp2, each containing a single active site DTG or DSG sequence can be produced independently as recombinant polypeptides, then combined in solution where they reconstitute an active protease.

Detailed Description Text (18):
Thus, the invention provides a purified polypeptide comprising a fragment of a mammalian Asp2 protein, wherein said fragment lacks the Asp2 transmembrane domain of said Asp2 protein, and wherein the polypeptide and the fragment retain the .beta.-secretase activity of said mammalian Asp2 protein. In a preferred embodiment, the purified polypeptide comprises a fragment of a human Asp2 protein that retains the .beta.-secretase activity of the human Asp2 protein from which it was derived. Examples include: a purified polypeptide that comprises a fragment of Asp2(a) having the amino acid sequence set forth in SEQ ID NO: 4, wherein the polypeptide lacks transmembrane domain amino acids 455 to 477 of SEQ ID NO: 4; a purified polypeptide as described in the preceding paragraph that further lacks cytoplasmic domain amino acids 478 to 501 of SEQ ID NO: 4; a purified polypeptide as described in either of the preceding paragraphs that further lacks amino acids 420-454 of SEQ ID NO: 4, which constitute a putative alpha helical region between the catalytic domain and the transmembrane domain that is believed to be

unnecessary for .beta.-secretase activity; a purified polypeptide that comprises an amino acid sequence that includes amino acids 58 to 419 of SEQ ID NO: 4, and that lacks amino acids 22 to 57 of SEQ ID NO: 4; a purified polypeptide that comprises an amino acid sequence that includes amino acids 46 to 419 of SEQ ID NO: 4, and that lacks amino acids 22 to 45 of SEQ ID NO: 4; a purified polypeptide that comprises an amino acid sequence that includes amino acids 22 to 454 of SEQ ID NO: 4. a purified polypeptide that comprises a fragment of Asp2(b) having the amino acid sequence set forth in SEQ ID NO: 6, and wherein said polypeptide lacks transmembrane domain amino acids 430 to 452 of SEQ ID NO: 6; a purified polypeptide as described in the preceding paragraph that further lacks cytoplasmic domain amino acids 453 to 476 of SEQ ID NO: 6; a purified polypeptide as described in either of the preceding two paragraphs that further lacks amino acids 395-429 of SEQ ID NO: 4, which constitute a putative alpha helical region between the catalytic domain and the transmembrane domain that is believed to be unnecessary for .beta.-secretase activity; a purified polypeptide comprising an amino acid sequence that includes amino acids 58 to 394 of SEQ ID NO: 4, and that lacks amino acids 22 to 57 of SEQ ID NO: 4; a purified polypeptide comprising an amino acid sequence that includes amino acids 46 to 394 of SEQ ID NO: 4, and that lacks amino acids 22 to 45 of SEQ ID NO: 4; and a purified polypeptide comprising an amino acid sequence that includes amino acids 22 to 429 of SEQ ID NO: 4.

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1: Proc Natl Acad Sci U S A. 1999 Jan 19;96(2):742-7.

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Endoplasmic reticulum and trans-Golgi network generate distinct populations of Alzheimer beta-amyloid peptides.

Greenfield JP, Tsai J, Gouras GK, Hai B, Thinakaran G, Checler F, Sisodia SS, Greengard P, Xu H.

Laboratory of Molecular and Cellular Neuroscience, and Fisher Center for Research on Alzheimer Disease, The Rockefeller University, 1230 York Avenue, New York, NY 10021, USA.

The excessive generation and accumulation of 40- and 42-aa beta-amyloid peptides (Abeta40/Abeta42) in selectively vulnerable brain regions is a major neuropathological feature of Alzheimer's disease. Abeta, derived by proteolytic cleavage from the beta-amyloid precursor protein (betaAPP), is normally secreted. However, recent evidence suggests that significant levels of Abeta also may remain inside cells. Here, we have investigated the subcellular compartments within which distinct amyloid species are generated and the compartments from which they are secreted. Three experimental approaches were used: (i) immunofluorescence performed in intact cortical neurons; (ii) sucrose gradient fractionation performed with mouse neuroblastoma cells stably expressing wild-type betaAPP695 (N2a695); and (iii) cell-free reconstitution of Abeta generation and trafficking from N2a695 cells. These studies demonstrate that: (i) Abeta40 (Abeta1-40 plus Abetax-40, where x is an NH2-terminal truncation) is generated exclusively within the trans-Golgi Network (TGN) and packaged into post-TGN secretory vesicles; (ii) Abetax-42 is made and retained within the endoplasmic reticulum in an insoluble state; (iii) Abeta42 (Abeta1-42 plus Abetax-42) is made in the TGN and packaged into secretory vesicles; and (iv) the amyloid peptides formed in the TGN consist of two pools (a soluble population extractable with detergents and a detergent-insoluble form). The identification of the organelles in which distinct forms of Abeta are generated and from which they are secreted should facilitate the identification of the proteolytic enzymes responsible for their formation.

PMID: 9892704 [PubMed - indexed for MEDLINE]

Related Links

Presenilin 1 regulates the processing of beta-amyloid precursor protein C-terminal fragments and the generation of amyloid beta-protein in endoplasmic reticulum and Golgi. [Biochemistry. 1998]

Subcellular compartment and molecular subdomain of beta-amyloid precursor protein relevant to the Abeta 42-promoting effects of Alzheimer mutant presenilin 2. [Neurobiol Dis. 2001]

Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. [J Neurosci. 2001]

Estrogen lowers Alzheimer beta-amyloid generation by stimulating trans-Golgi network vesicle biogenesis. [J Biol Chem. 2002]

Effects of neprilysin chimeric proteins targeted to subcellular compartments on amyloid beta peptide clearance in primary neurons. [J Biol Chem. 2004]

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1: Nat Med. 1997 Sep;3(9):1016-20.

Distinct sites of intracellular production for Alzheimer's disease A beta40/42 amyloid peptides.

Hartmann T, Bieger SC, Bruhl B, Tienari PJ, Ida N, Allsop D, Roberts GW, Masters CL, Dotti CG, Unsicker K, Beyreuther K.

Zentrum fur Molekulare Biologie der Universitat Heidelberg (ZMBH), Germany.

The Alzheimer amyloid precursor protein (APP) is cleaved by several proteases, the most studied, but still unidentified ones, are those involved in the release of a fragment of APP, the amyloidogenic beta-protein A beta. Proteolysis by gamma-secretase is the last processing step resulting in release of A beta. Cleavage occurs after residue 40 of A beta [A beta(1-40)], occasionally after residue 42 [A beta(1-42)]. Even slightly increased amounts of this A beta(1-42) might be sufficient to cause Alzheimer's disease (AD) (reviewed in ref. 1, 2). It is thus generally believed that inhibition of this enzyme could aid in prevention of AD. Unexpectedly we have identified in neurons the endoplasmic reticulum (ER) as the site for generation of A beta(1-42) and the trans-Golgi network (TGN) as the site for A beta(1-40) generation. It is interesting that intracellular generation of A beta seemed to be unique to neurons, because we found that nonneuronal cells produced significant amounts of A beta(1-40) and A beta(1-42) only at the cell surface. The specific production of the critical A beta isoform in the ER of neurons links this compartment with the generation of A beta and explains why primarily ER localized (mutant) proteins such as the presenilins could induce AD. We suggest that the earliest event taking place in AD might be the generation of A beta (1-42) in the ER.

PMID: 9288729 [PubMed - indexed for MEDLINE]

Related Links

Presenilin 1 regulates processing of beta-am precursor protein C-te fragments and the ge of amyloid beta-protei endoplasmic reticulum Golgi. [Biochemis

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1: Nat Med. 1997 Sep;3(9):1021-3.

Alzheimer's A beta(1-42) is generated in the endoplasmic reticulum/intermediate compartment of NT2N cells.

Cook DG, Forman MS, Sung JC, Leight S, Kolson DL, Iwatsubo T, Lee VM, Doms RW.

Department of Pathology & Laboratory Medicine, University of Pennsylvania, Abramson Research Center, Philadelphia 19104, USA.

Alzheimer's disease (AD) is a neurodegenerative disorder involving the florid deposition of vascular and cerebral plaques composed chiefly of amyloid beta-peptide (A beta) derived from cleavage of the amyloid precursor protein (APP). Varying in length from 39 to 43 amino acids, A beta, particularly the longer A beta (42), is thought to play a significant role in AD pathogenesis. To better understand AD it is important to identify the subcellular organelles generating A beta. Studies using agents that disrupt endosomal/lysosomal function suggest that A beta is generated late in the secretory and endocytic pathways. However, much of what is known about A beta biosynthesis has been inferred by monitoring extracellular A beta levels since intracellular A beta is undetectable in most cell types. Consequently, the precise site or sites that generate A beta, or whether A beta(1-40) and A beta(1-42) are generated at the same point in the biosynthetic pathway, is not known. Using human NT2N neurons, we found that retention of APP in the endoplasmic reticulum/intermediate compartment (ER/IC) by three independent approaches eliminated production of intracellular A beta(1-40), but did not alter intracellular A beta(1-42) synthesis. These findings suggest that the ER/IC may be an important site for generating this highly amyloidogenic species of A beta.

PMID: 9288730 [PubMed - indexed for MEDLINE]

Related Links

A distinct ER/IC gamm secretase competes w proteasome for cleava APP. [Biochemis

Presenilins are not rec A beta 42 production i early secreto[illegible]

Expression of beta-am precursor protein-CD3 chimeras to demonstr selective generation o beta(1-40) and amylo (1-42) peptides within secretory and endocyt compartments[J Biol Ch

Novel beta-secretase of beta-amyloid precu protein in the endopla reticulum/intermediat compartment of [illegible]

Distinct sites of intrac production for Alzheim disease A beta40/42 a peptides. [Nat M

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           42662   FILE DGENE
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L2           831 S L1 AND TRANSMEMBRANE
L3            42 S L2 AND PD=<1997
L4             8 DUP REM L3 (34 DUPLICATES REMOVED)
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L4 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 1997:56953 CAPLUS
DOCUMENT NUMBER: 126:141149
TITLE: Ectodomain phosphorylation of β-amyloid precursor protein at two distinct cellular locations
AUTHOR(S): Walter, Jochen; Capell, Anja; Hung, Albert Y.; Langen, Hanno; Schnoelzer, Martina; Thinakaran, Gopal; Sisodia, Sangram S.; Selkoe, Dennis J.; Haass, Christian
CORPORATE SOURCE: Dep. Molecular Biology, Inst. Mental Health, Mannheim, 68159, Germany
SOURCE: Journal of Biological Chemistry (1997), 272(3), 1896-1903
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The β-amyloid precursor protein (βAPP) is a transmembrane protein that is exclusively phosphorylated on serine residues within its ectodomain. To identify the cellular site of βAPP phosphorylation, we took advantage of an antibody that specifically detects the free C terminus of .beta.-secretase-cleaved βAPP containing the Swedish missense mutation (APPssw-β). This antibody previously established the cellular location of the .beta.-secretase cleavage of Swedish βAPP as a post-Golgi secretory compartment (Haass, C., Lemere, C., Capell, A., Citron, M., Seubert, P., Schenk, D., Lannfelt, L., and Selkoe, D. J. (1995) Nature Med. 1, 1291-1296). We have now localized the selective ectodomain phosphorylation of βAPP to the same compartment. Moreover, the phosphorylation sites of βAPP were identified at Ser198 and Ser206 of βAPP695 by tryptic peptide mapping, mass spectrometry, and site-directed mutagenesis. Intracellular phosphorylation of βAPP was inhibited by Brefeldin A and by incubating cells at 20°, thus excluding phosphorylation in the endoplasmic reticulum or trans-Golgi network. Ectodomain phosphorylation within a post-Golgi compartment occurred not only with mutant Swedish βAPP, but also with wild type βAPP. In addition to phosphorylation within a post-Golgi compartment, βAPP was also found to undergo phosphorylation at the cell surface by an ectoprotein kinase. Therefore, this study revealed two distinct cellular locations for βAPP phosphorylation.
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 1996:304685 CAPLUS
DOCUMENT NUMBER: 125:2465
TITLE: APP gene family: alternative splicing generates functionally related isoforms
AUTHOR(S): Sandbrink, R.; Masters, C. L.; Beyreuther, K.
CORPORATE SOURCE: Zentrum Molekulare Biologie Heidelberg, University of Heidelberg, Heidelberg, D-69120, Germany
SOURCE: Annals of the New York Academy of Sciences (1996), 777(Neurobiology of Alzheimers Disease), 281-287
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Alzheimer's βA4-amyloid protein precursor (APP) and the APP-like proteins (APLPs) are transmembrane glycoproteins with a similar

modular domain structure. APP exists in 8 isoforms generated by alternative splicing of exons 7, 8, and 15, of which the L-APP mRNAs lacking exon 15 are ubiquitously expressed in rat tissues but not in neurons. Rat APLP2, the nearest relative of APP, is similarly expressed in 4 different isoforms due to alternative splicing of inserts encoding a Kunitz protease inhibitor domain (KPI, homologous to exon 7 of APP) and a divergent region of 12 amino acids on the NH2-terminal side of the transmembrane domain (12 aa exon). KPI-APLP2 transcripts are highly expressed in neurons, in contrast to KPI-APPs, while L-APLP2 mRNA isoforms lacking the 12 aa exon are predominantly expressed in non-neuronal rat tissues, similar to L-APPs. Further examination of the divergent domains in APP and APLP2 harboring the similarly alternatively spliced APP exon 15 and the 12 aa exon of APLP2 revealed some structural similarities of the amino acid sequences and the predicted secondary structures. In both L-APLP2 and L-APP, a putative xylosyl-transferase recognition site for chondroitin sulfate glycosaminoglycan attachment is present that is interrupted in APP and APLP2 isoforms expressing APP exon 15 or the 12 aa exon of APLP2. Thus, a related function of the divergent domains and the corresponding alternatively spliced APP and APLP2 isoforms in regulation of the binding properties of the ectodomain is suggested. Addnl., .beta.-secretase cleavage of APP might be sterically hindered selectively in proteoglycan L-APP but not in APP lacking the proteoglycan attachment site. Neurons which have a uniquely low portion of L-APP and high content of APP might therefore be especially susceptible to βA4-protein liberation. This could explain the selective vulnerability of neurons that is observed in Alzheimer's disease.

L4 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 1996:304668 CAPLUS
DOCUMENT NUMBER: 125:6770
TITLE: The role of APP processing and trafficking pathways in the formation of amyloid β-protein
AUTHOR(S): Selkoe, D. J.; Yamazaki, T.; Citron, M.; Podlisny, M. B.; Koo, E. H.; Teplow, D. B.; Haass, C.
CORPORATE SOURCE: Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, MA, 02115, USA
SOURCE: Annals of the New York Academy of Sciences (1996), 777(Neurobiology of Alzheimers Disease), 57-64
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 19 refs. The amyloid β-protein (Aβ) is a proteolytic fragment of the β-amyloid precursor protein (βAPP). The authors previously reported the constitutive secretion of Aβ peptides from a variety of cells expressing βAPP under normal culture conditions. These endogenously produced Aβ peptides have heterogeneous N- and C-termini that vary as a function of βAPP missense mutations. Treatment of Aβ-secreting cells with agents that alter intravesicular pH showed that an acidic compartment is required for proper Aβ generation. One such compartment appears to be the endosome. Immunolabeling of cell-surface βAPP in living neurons and non-neuronal cells directly demonstrated the endocytosis of the protein and its rapid recycling (within 5-10 min) to the cell surface, as well as the trafficking of some βAPP to lysosomes. Expression of βAPP with various deletions of the cytoplasmic domain, including the NPTY motif, leads to decreased internalization and an associated decrease in the production of Aβ peptides that begin at the usual asp1 start site. These and other data suggest that Aβ production begins with cleavage of βAPP by a still unknown protease(s) (. beta.-secretase[s]) at the met-asp bond preceding the Aβ N-terminus and that this occurs in part in early endosomes. To characterize the substrate requirements of .beta.-secretase, βAPP

was mutagenized by placing stop codons within or at the end of the transmembrane domain or substituting other amino acids for the wild-type met and asp at the P1 and P1' positions. These expts. showed that proper .beta.-secretase cleavage requires the precursor to be membrane-anchored and is highly sequence specific; most substitutions at met or asp substantially decrease Aβ production Analogous mutagenesis expts. around the Aβ C-terminus revealed that the unknown protease(s) cleaving here ("γ-secretase[s]") does not show such specificity. Cells secreting Aβ may also be useful for examining the critical issue of the aggregation of Aβ into its neurotoxic polymeric form under physiol. conditions. In this regard, the authors have found that βAPP-expressing CHO cells show aggregation of ≥ 10-20% of their secreted Aβ peptides into SDS-stable dimers, trimers and sometimes tetramers under normal culture conditions. The identity of these small multimers was confirmed by extensive immunochem. characterization and radiosequencing. They are present atomic

L4 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 1995:388872 CAPLUS
DOCUMENT NUMBER: 122:184656
TITLE: Basolateral secretion of amyloid precursor protein in Madin-Darby canine kidney cells is disturbed by alterations of intracellular pH and by introducing a mutation associated with familial Alzheimer's disease
AUTHOR(S): De Strooper, Bart; Craessaerts, Katleen; Dewachter, Ilse; Moechars, Dieder; Greenberg, Barry; Van Leuven, Fred; Van Den Berghe, Herman
CORPORATE SOURCE: Cent. Human Gen., KULeuven, Louvain, B-3000, Belg.
SOURCE: Journal of Biological Chemistry (1995), 270(8), 4058-65
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The anal. of potential sorting signals in amyloid precursor protein (APP) by site-directed mutagenesis and the disturbance of metabolic pathways by drugs is used here to define the parameters that determine polarized secretion of APP in Madin-Darby canine kidney cells. Endogenously produced APP 751/770 and APP 695 produced from transfected constructs are secreted almost exclusively into the basolateral compartment. The sorting mechanism is highly dependent on intracellular pH as demonstrated by its sensitivity to primary amines and inhibitors of the acidifying vacuolar proton ATPase. The role of potential basolateral sorting signals in the cytoplasmic, transmembrane, and βA4 amyloid region of APP was investigated. Neither deletion of the endocytosis and putative basolateral sorting signal GY.NPTY nor complete deletion of the cytoplasmic domain causes apical secretion of soluble APP. Further deletion of the transmembrane domain and of the βA4 amyloid region confirmed that the major basolateral sorting determinant resides in the extracellular domain of APP. Increased .beta.-secretase cleavage of APP after introduction of the "swedish" double mutation causes apical missorting of about 20% of .beta.-secretase -cleaved APP. The data underline the complexity of processing and sorting APP in polarized cells and suggest a possible problem of protein sorting in Alzheimer's Disease.

L4 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1995:469448 CAPLUS
DOCUMENT NUMBER: 122:210831
TITLE: Role of the β-amyloid protein in Alzheimer's disease
AUTHOR(S): Sisodia, Sangram S.; Price, Donald L.
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205,

USA
SOURCE: FASEB Journal (1995), 9(5), 366-70
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 77 refs. The principal component of amyloid is the β-amyloid protein (Aβ), a 39-43 amino acid peptide composed of a portion of the transmembrane domain and the extracellular domain of the amyloid precursor protein (APP). APP occurs as several Aβ-containing isoforms of 695, 751, and 770 amino acids, with the latter two APP containing a domain that shares structural and functional homologies with Kunitz serine protease inhibitors. In cultured cells, APP mature through the constitutive secretory pathway, and some cell surface-bound APP are cleaved by an enzyme, designated as α-secretase, within the Aβ domain, an event that precludes Aβ amyloidogenesis. Several studies have delineated two addnl. pathways of APP processing: first, an endosomal/lysosomal pathway generates a complex set of APP-related membrane-bound fragments, some of which contain the entire Aβ sequence; and, second, by mechanisms which are not fully understood, Aβ1-40 is secreted into the conditioned medium in vitro and is present in cerebrospinal fluid in vivo. The intracellular sites of enzymes responsible for proteolytic cleavage at the NH2 and COOH termini of Aβ, termed γ- and . beta.-secretase, resp., have not been identified. Finally, recent mol. genetic investigations have identified a variety of mutations in APP that segregate with early-onset familial AD and with hereditary cerebral hemorrhage with amyloid, Dutch type (HCHWA-D). Several of these mutations appear to influence APP processing and result in the production of higher levels or longer Aβ-related peptides that are inherently more fibrillogenic. Although a variety of lines of evidence implicates APP/Aβ in AD, the mechanisms by which Aβ influences the biol. and vulnerability of neural cells are not fully understood but are very active areas of investigation. This review focuses on the present state of our understanding of APP and Aβ in the context of AD.

L4 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 1995:786876 CAPLUS
DOCUMENT NUMBER: 123:224499
TITLE: The metabolism of the amyloid precursor protein and its relevance to Alzheimer's disease
AUTHOR(S): Sinha, Sukanto
CORPORATE SOURCE: Athena Neurosciences, San Francisco, CA, 94080, USA
SOURCE: Perspectives in Drug Discovery and Design (1995), 2(3), 363-9
CODEN: PDDDEC; ISSN: 0928-2866
PUBLISHER: ESCOM
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review and discussion with 41 refs. The pathol. of Alzheimer's disease is primarily characterized by the deposition of β-amyloid/Aβ peptide as the major component of senile or neuritic plaques. The Aβ peptide is produced as a result of proteolytic cleavage of the transmembrane protein precursor, APP, during its normal cellular metabolism The free amino terminus of the Aβ peptide is generated by an endopeptidic cleavage between Met671-Asp672 by a protease termed . beta.-secretase. Increased cleavage at this site takes place in a rare, inherited double mutation (Lys670-Met671 to Asn670-Leu671), leading to increased Aβ production and consequent development of Alzheimer's disease on an accelerated time scale in the affected individuals, underscoring the pathol. importance of .beta .-secretase activity. Cellular studies provide direct evidence that inhibition of .beta.-secretase activity would

appear to be effective in inhibiting Aβ production as a rational approach to developing therapeutics for the disease.

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ACCESSION NUMBER: 1995:542911 SCISEARCH
THE GENUINE ARTICLE: RP189
TITLE: AMYLOID-BETA AMYLOIDOSIS IN ALZHEIMERS-DISEASE
AUTHOR: PRICE D L (Reprint); SISODIA S S; GANDY S E
CORPORATE SOURCE: JOHNS HOPKINS UNIV, SCH MED, NEUROPATHOL LAB, 558 ROSS RES BLDG, 720 RUTLAND AVE, BALTIMORE, MD 21205 (Reprint); JOHNS HOPKINS UNIV, SCH MED, DEPT PATHOL, BALTIMORE, MD 21205; JOHNS HOPKINS UNIV, SCH MED, DEPT NEUROL, BALTIMORE, MD 21205; JOHNS HOPKINS UNIV, SCH MED, DEPT NEUROSCI, BALTIMORE, MD 21205; CORNELL UNIV, MED CTR, NEW YORK HOSP, DEPT NEUROL, NEW YORK, NY 10021; CORNELL UNIV, MED CTR, NEW YORK HOSP, DEPT NEUROSCI, NEW YORK, NY 10021
COUNTRY OF AUTHOR: USA
SOURCE: CURRENT OPINION IN NEUROLOGY, (AUG 1995) Vol. 8, No. 4, pp. 268-274.
ISSN: 1350-7540.
PUBLISHER: CURRENT SCIENCE, 400 MARKET STREET,SUITE 750 ATTN:SARAH WHEALEN/SUB MGR, PHILADELPHIA, PA 19106.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 71
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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The presence of amyloid deposits in the parenchyma of the amygdala, hippocampus, and neocortex is a major histopathological hallmark of Alzheimer's disease. The principal component of amyloid is amyloid beta, a 39-43 amino acid peptide comprised of a portion of the transmembrane domain and the extracellular domain of the amyloid precursor proteins. Amyloid precursor proteins occur as several amyloid beta-containing isoforms of 695, 751, and 770 amino acids. In cultured cells, amyloid precursor proteins mature through the constitutive secretory pathway, and some cell-surface-bound amyloid precursor proteins are cleaved by an enzyme, designated as alpha-secretase, within the amyloid beta domain, an event that precludes amyloid beta amyloidogenesis. Two additional pathways of amyloid precursor protein processing include an endosomal/lysosomal pathway that generates a complex set of amyloid precursor protein-related membrane-bound fragments, some of which contain the entire amyloid beta sequence; and, by mechanisms not fully understood, secretion of amyloid beta 1-40 into the conditioned medium in vitro and its presence in cerebrospinal fluid in vivo. The intracellular sites of enzymes responsible for proteolytic cleavage at the amino- and carboxyl-termini of amyloid beta, termed gamma- and beta-secretase, respectively, have not been identified. Molecular genetic investigations have identified a variety of mutations in the amyloid precursor protein gene that segregate with early-onset familial Alzheimer's disease and with hereditary cerebral hemorrhage with amyloid, Dutch type. Several of these mutations appear to influence amyloid precursor protein processing and result in the production of higher levels or longer amyloid beta-related peptides that are inherently more fibrillogenic. Although a variety of lines of evidence implicate amyloid precursor protein and amyloid beta in Alzheimer's disease, the mechanism(s) by which amyloid beta influences the biology and vulnerability of neural cells is not fully clear. Amyloid beta toxicity is being explored in vitro and in vivo. Finally, recent progress has been made in the generation of transgenic mice expressing amyloid precursor protein or amyloid beta that recapitulate a subset of the pathology observed in Alzheimer's disease.

L4 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 1993:647525 CAPLUS
DOCUMENT NUMBER: 119:247525
TITLE: Glycoprotein E1 of hog cholera virus expressed in insect cells protects swine from hog cholera
AUTHOR(S): Hulst, M. M.; Westra, D. F.; Wensvoort, G.; Moormann, R. J. M.
CORPORATE SOURCE: Virol. Dep., Cent. Vet. Inst., Lelystad, 8200 AJ, Neth.
SOURCE: Journal of Virology (1993), 67(9), 5435-42
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The processing and protective capacity of E1, an envelope glycoprotein of hog cholera virus (HCV), were investigated after expression of different versions of the protein in insect cells by using a baculovirus vector. Recombinant virus BacE1[+] expressed E1, including its C-terminal transmembrane region (TMR), and generated a protein which was similar in size (51-54 kDa) to the size of E1 expressed in swine kidney cells infected with HCV. The protein was not secreted from the insect cells, and like wild-type E1, it remained sensitive to endo-β-N-acetyl-D-glucosaminidase H (endo H). This indicates that E1 with a TMR accumulates in the endoplasmic reticulum or cis-Golgi region of the cell. In contrast, recombinant virus BacE1[-], which expressed E1 without a C-terminal TMR, generated a protein that was secreted from the cells. The fraction of this protein that was cell-associated had a slightly lower mol. mass (49-52 kDa) than wild-type E1 and remained endo H sensitive. The high-mannose units of the secreted protein were trimmed during transport through the exocytotic pathway to endo H-resistant glycans, resulting in a protein with a lower mol. mass (46-48 kDa). Secreted E1 accumulated in the medium to about 30 μg/106 cells. This amount was about 3-fold higher than that of cell-associated E1 in BacE1[-] and 10-fold higher than that of cell-associated E1 in BacE1[+]-infected Sf21 cells. I.m. vaccination of pigs with immunoaffinity-purified E1 in a double water-oil emulsion elicited high titers of neutralizing antibodies between 2 and 4 wk after vaccination at the lowest dose tested (20 μg). The vaccinated pigs were completely protected against intranasal challenge with 100 50% LDs of HCV strain Brescia, indicating that E1 expressed in insect cells is an excellent candidate for development of a new, safe, and effective HCV subunit vaccine.